

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of irreversible electroporation for the treatment of liver metastases

Treating cancer that has spread to the liver using focused electrical fields

When cancer has spread from other parts of the body to the liver the tumours are called liver metastases. Irreversible electroporation is a process that uses electrical fields to kill cancer cells. It is applied directly to the tumour through special needles. The main difference between this procedure and thermal techniques for destroying liver metastases is that it does not produce extreme heat or cold.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in January 2012.

Procedure name

- Irreversible electroporation for the treatment of liver metastases

Specialty societies

- Royal College of Radiologists
- British Society of Interventional Radiology
- British Society of Gastrointestinal and Abdominal Radiology
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- British Association of Surgical Oncology (cancer surgery).

Description

Indications and current treatment

Liver metastases are most commonly caused by the spread of colorectal cancer but they may also result from other malignancies, such as lung and gastric cancer. For a minority of patients, surgical resection with curative intent may be possible. However, treatment depends on the extent and location of the liver metastases, and for most patients treatment intent is palliative.

Options for palliative treatment include systemic chemotherapy, external beam radiotherapy, transcatheter chemoembolisation, other thermal ablation techniques (such as cryotherapy, radiofrequency or microwave ablation), arterial embolism techniques and selective internal radiation therapy. Multiple treatments may be used for individual patients.

Electroporation is a non-thermal technique that increases cell membrane permeability by changing the transmembrane potential and subsequently disrupting the integrity of the lipid bilayer. Irreversible electroporation (IRE) is the stage at which the electrical field has been applied with sufficient amplitude and duration to cause permanent disruption of cell membrane integrity, resulting in cell death. The key difference between IRE and thermal ablation techniques is that it does not produce extreme heat or cold. It may selectively damage cancerous cells while sparing supporting connective tissue, for example nearby blood vessels and nerves, allowing a more targeted treatment compared with other types of treatment.

What the procedure involves

Cancerous cells are subjected to a powerful electrical field using high-voltage direct current (up to 3 kV). This creates multiple holes in the cell membrane, irreversibly damaging homeostasis mechanisms and leading to cell death.

The procedure is done with the patient under general anaesthesia. A neuromuscular blocking agent is administered to prevent muscle spasms. Once the patient has been anaesthetised and placed in the appropriate position for best access to the target tumour, an intravenous contrast medium-enhanced computed tomography (CT) scan is carried out. Bipolar or unipolar electrode needles are introduced percutaneously and guided into place in and adjacent to the target tumour under CT and/or ultrasound image guidance. The distance between the electrodes is confirmed by CT and/or ultrasound imaging to ensure that the electrodes were correctly placed parallel to one another and that sufficient current flow would be generated to ensure IRE. The procedure may also be performed through open surgical, or laparoscopic approaches.

Each ablation cycle consists of pulses of high-voltage direct current delivered in groups (of about 10) with a brief time for recharging between groups (a cycle is usually completed in less than 2 minutes). Electrodes are repositioned

under imaging guidance to extend the zone of electroporation until the entire tumour and an appropriate margin have been ablated. The number of ablations is determined by the volume of the target tumour. When the ablation procedure is completed, another intravenous contrast medium-enhanced CT scan may be carried out to confirm that the entire target region has been ablated. Total procedure time has been reported to range between 2.5 and 4.5 hours.

Cardiac synchronisation is used to minimise the risk of arrhythmias. Precautions should be taken for patients with implantable electrical devices. Ablation of lesions in the vicinity of implanted electronic devices or implanted devices with metal parts should be avoided. It is important to ensure that interventions (such as a defibrillator) and people trained to treat cardiac arrhythmias are available.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to Irreversible electroporation for the treatment of liver metastases. Searches were conducted of the following databases, covering the period from their commencement to 19 January 2012: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. Language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with liver metastases.
Intervention/test	Irreversible electroporation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 160 patients from 4 case series¹⁻⁴, 2 case reports⁵⁻⁶ and data from an unpublished register.

Table 2 Summary of key efficacy and safety findings on irreversible electroporation for the treatment of liver metastases

Abbreviations used: ALT, alanine aminotransferase; CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation																									
Study details		Key efficacy findings		Key safety findings	Comments																				
Thomson KR (2011) ¹ Case series Australia Recruitment period: 2008–9 Study population: Patients with 1 or more tumours of the target organs (liver, lung and kidney). n = 38 patients; 69 IRE procedures Age: not reported Sex: not reported Patient selection criteria: Indications: Patients with 1 or more tumours of the target organs (liver, lung and kidney) in which conventional therapy was not possible or had been unsuccessful. Contraindications include cardiac failure, recent liver embolisation and imminent liver failure from tumour load. Technique: IRE was performed with the patients under general anaesthesia		Number of patients analysed: 37 Number of patients treated with IRE for liver metastases = 32.4% (12/37); 45 procedures (figures calculated from table 2 of the paper). Response rate IRE response rate in liver metastases was 50% but all patients in this group showed progressive disease from other lesions (actual numbers not reported; ‘response rate’ was not defined; exact timing of assessment unclear). Outcome* of the 45 procedures performed in 12 patients with liver metastases: <table><tr><td></td><td>Number of procedures</td></tr><tr><td>Complete response</td><td>19</td></tr><tr><td>Progressive disease</td><td>20</td></tr><tr><td>Stable disease</td><td>6</td></tr></table> * Assessed by modified response evaluation criteria in solid tumours (RECIST) at 3 months. Liver metastases larger than 5 cm in any dimension showed no response in terms of tumour control. Biopsy of a colorectal carcinoma metastasis that had not changed in size (non-enhancing on CT) showed coagulative necrosis with patent blood vessels.			Number of procedures	Complete response	19	Progressive disease	20	Stable disease	6	Key safety findings potentially related to use of IRE for liver metastases: <table><tr><td></td><td>No. reported</td></tr><tr><td>ALT levels increases of between 19 and 1747 U/L at 24 hours post-IRE^a</td><td>95.2% (40/42^c) of liver tumour ablation procedures</td></tr><tr><td>Transient increase in bilirubin level^b</td><td>18.4% (9/49^c) of liver tumour ablation procedures</td></tr></table> ^a Levels returned to normal or baseline levels at 1-month follow-up in 97.5% (39/40) of the procedures. One patient with progressive disease had an increased ALT level compared with baseline at 3-month follow-up. No increase was observed in two cases in which review of IRE output data suggested current flow had not occurred. ^b Returned to normal or baseline levels observed at 1-month follow-up. ^c ALT levels were only available for 42 of 49 liver tumour ablation procedures. Key safety findings related to use of IRE (unclear treatment is specifically for liver metastases): <table><tr><td></td><td>Number reported</td></tr><tr><td>Mortality at 30 days</td><td>None</td></tr><tr><td>Transient ventricular arrhythmia (with inadequate ECG synchronisation)^{c, d}</td><td>4 patients (no treatment needed, transient)</td></tr></table>		No. reported	ALT levels increases of between 19 and 1747 U/L at 24 hours post-IRE ^a	95.2% (40/42 ^c) of liver tumour ablation procedures	Transient increase in bilirubin level ^b	18.4% (9/49 ^c) of liver tumour ablation procedures		Number reported	Mortality at 30 days	None	Transient ventricular arrhythmia (with inadequate ECG synchronisation) ^{c, d}	4 patients (no treatment needed, transient)	Follow-up issues: - One patient with advanced lung cancer was lost to follow-up at 1 month and 3 months after discharge. Study design issues: - This study was designed to report outcomes in the first human treatments with IRE. - No formal statistical tests were performed for data on outcome (whether there was complete response, progressive disease or stable disease). - There was no formal assessment of pain as this was proxy-defined as the need for analgesic agents. Study population issues: - Study recruited and reported patients with different tumours, not specific to liver metastases. Consequently, some of the safety findings
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Progressive disease	20																								
Stable disease	6																								
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Study details	Key efficacy findings	Key safety findings		Comments
with muscle paralysis. Adequate cardiac synchronisation was achieved with AccuSync model 72. This was used after 4 patients reported cardiac arrhythmias with AccuSync model 42 R-wave trigger device. Follow-up: 3 months Conflict of interest/source of funding: One author or his department received funding/sponsorship from AngioDynamics (Queensbury, New York). None of the other authors have identified a conflict of interest.	Regeneration of liver Patients who did not have severe cirrhosis or previous chemoembolisation exhibited regeneration of liver after the procedure. Length of hospital stay Four patients had an in-hospital stay longer than 24 hours.	Transient supraventricular tachycardia (with adequate ECG synchronisation) ^d	1 patient (resolved without treatment)	highlighted may not relate to patients with liver metastases. Other issues: - Percentages for ‘upper-limb neurapraxia on recovery’ safety findings were not calculated. This is because the actual number of patients who had their arms extended above their head during the anaesthetic position for liver tumour ablation was not reported. It is in this position that patients are more likely to report neurapraxia. Subsequent positioning of patients’ arms in flexion with the use of foam pads reported no further cases of upper-limb neurapraxia. - There was inconsistency in reporting of the total number of patients who have received IRE for both primary and secondary liver tumours between figures presented in the tables (1 and 2) of the paper and the text. Figures calculated from the
		Atrial fibrillation (with adequate ECG synchronisation) ^d	1 patient (needed cardioversion)	
		Upper-limb neurapraxia on recovery	2 patients ^e (resolved at 1- and 3-month review without treatment)	
		Pneumothorax	4.3% (3/69) of procedures (One related to liver ablation; a Heimlich valve was inserted with resolution ‘in a few hours’)	
		Post-procedural pain needing prolonged pain relief after discharge ^f	None	
		Non-target organ damage, bile leaks, strictures, or vascular thrombosis	None	
^c Cardiac arrhythmia leading to procedures being aborted before completion of the planned number of ablations occurred in 2 procedures (blood pressure dropped but all symptoms resolved on stopping treatment). In addition, one of these four patients developed bigeminy after resolution of ventricular tachycardia, which resolved within 24 hours without treatment. Percentages not calculated because the actual number of patients who had undergone IRE without adequate ECG-synchronisation was not				

Abbreviations used: ALT, alanine aminotransferase; CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation			
Study details	Key efficacy findings	Key safety findings	Comments
		reported. ^d Timing unclear, most likely intraprocedural. ^e Both patients had their arms extended above their head during the anaesthetic procedure for liver tumour ablation. ^f One patient with hepatic epithelioid hemangioendothelioma reported severe pain in the right upper abdomen and shoulder, presumably related to minor hepatic subcapsular bleeding, although there was no evidence of bleeding on the post-procedural CT scan and the pain resolved in 48 hours without treatment other than opiate analgesic agents. Key safety findings related to use of IRE (treatment not for liver metastases) One patient treated for an upper-pole renal lesion reported partial ureteric obstruction and increased creatinine level after IRE. Creatinine returned to normal after insertion of a stent. Transient haematuria reported in 2 patients undergoing renal procedures. One patient treated for a left upper-pole renal lesion had an unplanned insertion of an electrode tip into the inferior portion of the left adrenal gland. This produced transient hypertension. The patient subsequently reported severe postural hypotension which lasted for 2 months. Other complications Two elderly patients who received IRE treatment to the liver had abnormal renal function before the procedure. They reported deterioration in renal function lasting as long as 6 months after receiving IRE. One patient experienced a brief flushing/allergic reaction after the procedure that appeared to be related to anaesthesia.	tables showed that 23 patients received 74 IRE procedures for treatment of their liver tumours on 62 occasions. The text reads 'IRE was performed for liver tumours on 63 occasions in 25 patients.' It was unclear how 'IRE response rate in liver metastases of 50%' as stated in the text was determined.

Abbreviations used: ALT, alanine aminotransferase; CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation																	
Study details	Key efficacy findings	Key safety findings	Comments														
Ball C (2010)² Case series Australia Recruitment period: not reported Study population: Patients with either primary or metastatic cancer, some in more than 1 site. n = 21 patients; 28 IRE procedures (17 hepatic tumours, 8 renal tumours; 3 lung tumours) Age: range 42–81 years Sex: not reported Patient selection criteria: not reported Technique: IRE was performed with the patients under general anaesthesia with muscle paralysis. All patients had intra-arterial blood pressure monitoring to detect arrhythmias. An ECG synchronisation device (AccuSync Model 72) was acquired early in the study with variable success with synchronisation. Follow-up: 24 to 48 hours	Not reported.	Key safety findings potentially related to use of IRE for liver metastases <table><tr><td></td><td>Procedures (% [n/n])</td></tr><tr><td>Significant but transient neurapraxia on recovery^a</td><td>16.7 (2/12)</td></tr><tr><td>Brief runs of ventricular tachycardia^b</td><td>25.0 (7/28)</td></tr><tr><td>Pneumothorax^c</td><td>10.7 (3/28)</td></tr><tr><td>Transient increase in systolic blood pressure of approximately 20 to 30 mm Hg after the treatment cycles^d</td><td>100 (all patients)</td></tr><tr><td>Postoperative pain</td><td>46.4 (13/28)</td></tr><tr><td>Acid-base disturbances with associated hyperkalaemia^e</td><td>14.3 (4/28)</td></tr></table> ^a All 12 patients were positioned supine with their arms extended above their heads during the procedure ^b Timing unclear, most likely intraprocedural. Arterial blood pressure was 'markedly decreased' in 4 of the 7 procedures. ^c Occurred because of insertion of the electrodes. One occurred after transabdominal placement of electrodes in the liver and two occurred in the lung treatment group. Two patients needed insertion of intercostal catheters to drain a pleural effusion as well as the pneumothorax (1) and pneumothorax alone (1). ^d This increase was not modified by opioids, was not sustained beyond a few minutes, and did not need treatment. ^e None of these patients had disturbances that were significant enough to limit the duration of the procedure. Other complications In inadequately paralysed patients, the discharge of the		Procedures (% [n/n])	Significant but transient neurapraxia on recovery ^a	16.7 (2/12)	Brief runs of ventricular tachycardia ^b	25.0 (7/28)	Pneumothorax ^c	10.7 (3/28)	Transient increase in systolic blood pressure of approximately 20 to 30 mm Hg after the treatment cycles ^d	100 (all patients)	Postoperative pain	46.4 (13/28)	Acid-base disturbances with associated hyperkalaemia ^e	14.3 (4/28)	Follow-up issues: - Patients were only followed up for 24 to 48 hours. Study design issues: - The CT scanning room was not initially designed for procedures needing anaesthesia and presented challenges of remote anaesthesia practice. Patients were transferred to the CT scanning machine after anaesthetic induction. The frequent travel of the CT scanning bed needed close attention to intravenous and intra-arterial lines and breathing circuit. - Formal method to assess postoperative pain not reported. - Study only reported safety findings but no reports on efficacy of IRE. Study population issues: - Study recruited and reported patients with different tumours, not specific to liver
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Study details	Key efficacy findings	Key safety findings	Comments
Conflict of interest/source of funding: One author received funding/sponsorship from the device manufacturer and a family member has a personal pecuniary interest. None of the other authors have identified a conflict of interest.		electrodes produced contractions of the entire upper body with each pulse, similar to that seen with a grand mal seizure (actual numbers not reported). When patients were adequately paralysed, some muscular contractions were still visible, mainly confined to the treatment area but sometimes including the diaphragm. These contractions are probably caused by direct muscle stimulation.	metastases. Consequently, the safety findings highlighted may not relate to patients with liver metastases only. It is likely that there is overlap of the patient population with Thomson KR (2011)¹. There is overlap in authorship and similar adverse events reported.

Abbreviations used: ALT, alanine aminotransferase; CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation													
Study details	Key efficacy findings	Key safety findings	Comments										
Hays D (2011)³ Retrospective case series Recruitment period: 2009–10 Study population: Patients were treated for lesions in the liver (33 lesions), lung (12 lesions), pelvis (3 lesions), lymph node (1 lesion) and pancreas (1 lesion). Average lesion size was 1.97 cm in the liver, 1.3 cm in the lung, 3.0 cm in the pelvis, 1.6 cm in the lymph nodes and 3.3 cm in the pancreas. n = 45 patients; 50 IRE procedures Age: range 42–84 years Sex: 55.6% (25/45) female Patient selection criteria: Exclusion criteria included atrial fibrillation and lesion size > 5 cm. Technique: IRE was performed with the patients under general anaesthesia using cardiac synchronisation. Follow-up: not reported	Number of patients analysed: 45 patients; 67 lesions; 50 IRE procedures ‘Technical success’ achieved in all 50 procedures. (‘Technical success’ was not defined; follow-up not stated) Length of hospital stay Mean length of hospital stay = 1.16 days (range 1–3 days)	One patient returned 4 days post-procedure with tachycardia, which resolved spontaneously. Overall complication rate: 24%. Procedural or immediate post-procedural complications include: <table><tr><td></td><td>Number reported</td></tr><tr><td>Pneumothorax^a</td><td>14% (7/50)</td></tr><tr><td>Transient intraprocedural hypertension</td><td>1 patient</td></tr><tr><td>Transient urinary retention</td><td>1 patient</td></tr><tr><td>Perianal fissure</td><td>1 patient</td></tr></table> ^a 12% (6/50) were treated with small calibre thoracostomy tubes. Not stated if patients were treated for lesions in the liver. Hospital readmission Readmission rate within 30 days after discharge = 2.0%		Number reported	Pneumothorax ^a	14% (7/50)	Transient intraprocedural hypertension	1 patient	Transient urinary retention	1 patient	Perianal fissure	1 patient	Conference abstract only Follow-up issues: - Patients were not followed up in the long term. Study design issues: - This is a retrospective study to evaluate the technical feasibility and clinical safety of IRE. Study population issues: - Study recruited and reported patients with different tumours. The underlying tumour treated was not described for all safety events.
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Pneumothorax ^a	14% (7/50)												
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Perianal fissure	1 patient												

Abbreviations used: ALT, alanine aminotransferase; CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation			
Study details	Key efficacy findings	Key safety findings	Comments
Thomson KR (2009)⁴ Case series Recruitment period: not reported Study population: Patients with lung, liver or kidney tumour. n = 18 procedures (12 liver tumours, 3 lung tumours, 3 renal tumours; 4 patients received more than 1 procedure) Age: not reported Sex: not reported Patient selection criteria: Patients with tumours not responsive to conventional therapy. Technique: Patients were placed under general anaesthesia. Electrodes were placed percutaneously in the target tumour under CT and ultrasound guidance. Follow-up: 30 day Conflict of interest/source of funding: not reported	Length of hospital stay The average length of stay was 24 hours. Patient response 94.4% (17/18) of the procedures were associated with a 'remarkable lack of symptoms' post-procedure (exact timing of assessment not stated). One patient continued a 'rapid decline' as a result of their tumour (exact timing of follow up not stated).	There was 1 event each of: • minor pneumothorax (not stated if patient was treated for liver tumour) • partial collapse of the right upper lobe related to bronchial compression by tumour • ventricular tachycardia associated with fall in blood pressure (timing unclear; ECG synchronisation was not used)	Conference abstract only Follow-up issues: • Follow-up CT at 30 days not yet completed in all patients at time of abstract submission but there was significant tumour reduction in most patients. Study design issues: • It was not reported whether patients were given muscle relaxants or whether ECG synchronisation were used. Study population issues: • Study recruited and reported patients with different tumours. It was unclear whether patients with lesions in the liver had liver metastases. Consequently, key efficacy and safety findings reported here are not specific/may not relate to patients with liver metastases. Other issues: • Likely to be an interim report of Thomson KR (2011)¹ with potential overlap of patients.

Abbreviations used: ALT, alanine aminotransferase; CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation			
Study details	Key efficacy findings	Key safety findings	Comments
Kasisivsanathan V (2011)⁵ Case report UK Recruitment period: not reported Study population: Single patient with liver metastasis. Age: not reported Sex: not reported Patient selection criteria: Patient with a solitary liver metastasis adjacent to the portal vein. Technique: IRE was carried out under general anaesthesia with muscle relaxation and electrical current was administered with ECG synchronisation. Follow-up: 1 month (not stated explicitly) Conflict of interest/source of funding: not reported	Patient response Complete tumour devascularisation was seen post-procedure and at 1 month, with no damage to the portal vein. Length of hospital stay Patient was discharged after 12 hours.	There were no periprocedural complications. Patient was discharged without needing any analgesia.	Conference abstract only This is a conference abstract on use of IRE on a single patient with a solitary liver metastasis. There was no detailed reporting of patient demographics.

Abbreviations used: ALT, alanine aminotransferase; CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation			
Study details	Key efficacy findings	Key safety findings	Comments
Deepika K (2011)⁶ Case report Recruitment period: not reported Study population: Single patient with metastatic liver tumour. Age: 65 years Sex: Female Patient selection criteria: not reported Technique: the patient was placed under general anaesthesia with muscle relaxation. Fentanyl analgesia was provided. Airway was secured with appropriate size endotracheal tube. IRE was done under CT imaging. Follow-up: not reported Conflict of interest/source of funding: not reported	Length of hospital stay Patient was discharged the same day upon full recovery from anaesthesia.	There was minimal blood loss.	Conference abstract only Study design issues: - The safety and success of IRE depends on accurate placement of probes under CT/ultrasound guidance. Therefore, considerations for anaesthesia outside operating room apply. Other issues: - The aim of this abstract was to present the anaesthetic management of the patient undergoing IRE procedure. Therefore, there were no other key efficacy and safety findings except as reported here.

Abbreviations used: ALT, alanine aminotransferase; CT, computed tomography; ECG, electrocardiography; IRE, irreversible electroporation																																																					
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Martin RCG (2012)⁷ ‘Soft tissue ablation’ (STAR) register dataset USA Recruitment period: 2009-11 Study population: patients with primary or secondary cancers in the liver n = 150 patients; 175 IRE procedures Age: not reported Sex: not reported Patient selection criteria: Patients receiving treatment for primary or secondary cancers in the liver. Technique: IRE was performed via an open (19.6%), laparoscopic (3.9%), or percutaneous (76.5%) approach. Follow-up: 12 months (median) Conflict of interest/source of funding: The STAR registry is partially funded by Angiodynamics as an unrestricted educational grant.	Number of patients analysed: 45 patients; 51 IRE procedures (65% for treatment of metastatic disease and 35% for treatment of hepatocellular carcinoma) Ablation success¹ <table><tr><th rowspan="2">Histology</th><th rowspan="2">No. of procedures</th><th rowspan="2">Ablation success (%)</th><th colspan="2">Ablation success (determined by Kaplan-Meier; %)</th></tr><tr><th>6 months</th><th>12 months</th></tr><tr><td>Metastatic colorectal liver cancer</td><td>22</td><td>95</td><td>94.1</td><td>58.8</td></tr><tr><td>Hepatocellular carcinoma</td><td>17</td><td>100</td><td>90.0</td><td>50.0</td></tr><tr><td>Other</td><td>12</td><td>100</td><td>100.0</td><td>100.0</td></tr><tr><td>P-value</td><td></td><td>0.523</td><td>0.573</td><td>0.573</td></tr></table> ¹Defined as complete eradication of visible disease at 3 months. Overall ablation success was maintained at 59.5% at 12 months. <u>Survival rate at 12-month</u> 5 patients with liver metastases and 3 patients with hepatocellular carcinoma died at 12-month. <u>Length of hospital stay</u> The median length of stay following ablation was 1 day.			Histology	No. of procedures	Ablation success (%)	Ablation success (determined by Kaplan-Meier; %)		6 months	12 months	Metastatic colorectal liver cancer	22	95	94.1	58.8	Hepatocellular carcinoma	17	100	90.0	50.0	Other	12	100	100.0	100.0	P-value		0.523	0.573	0.573	<u>Adverse events occurring in the first 90 days post-treatment</u> <table><tr><th>Histology</th><th>No. of procedures</th><th>Patients who had adverse events (%)</th><th>Calculated no. of patients who had adverse events</th></tr><tr><td>Metastatic colorectal liver cancer</td><td>22</td><td>9.1</td><td>2</td></tr><tr><td>Hepatocellular carcinoma</td><td>17</td><td>5.9</td><td>1</td></tr><tr><td>Other*</td><td>12</td><td>16.7</td><td>2</td></tr><tr><td>P-value</td><td></td><td>0.706</td><td></td></tr></table> * Liver metastases secondary to renal, lung and carcinoid tumours. A total of 9 adverse events occurred in 5 (9.8%). All were resolved (duration of adverse events not reported). Some adverse events needed intervention. - Two were deemed unrelated to the ablation (leukocytosis, urinary tract infection) - Four were categorised as indirectly related (dehydration, biliary stent occlusion, cholangitis caused by biliary stent occlusion, and acute renal failure) - Three were possibly procedure related (neurogenic bladder, abdominal pain, and flank pain) - There were no treatment-related deaths		Histology	No. of procedures	Patients who had adverse events (%)	Calculated no. of patients who had adverse events	Metastatic colorectal liver cancer	22	9.1	2	Hepatocellular carcinoma	17	5.9	1	Other*	12	16.7	2	P-value		0.706		Study population issues: A total of 150 patients with primary or secondary cancers in the liver had undergone IRE procedures. However, only 45 patients (51 IRE procedures) had been analysed at the time of presentation to NICE. Other issues: - Unpublished STAR register data obtained from an abstract which has been sent by the director of the register. - Details of interventions needed to treat adverse events were not specified.
	Histology	No. of procedures	Ablation success (%)				Ablation success (determined by Kaplan-Meier; %)																																														
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Efficacy

Response rate

In a case series of 38 patients (including 69 procedures for tumours in the liver, lung and kidney), a response rate of 50% was reported in 45 procedures performed for the treatment of liver metastases (actual numbers not reported; 'response rate' was not defined; exact timing of assessment unclear)¹. Liver metastases larger than 5 cm in any dimension showed no response in terms of tumour control and all patients with liver metastases had other lesions which progressed.

Safety

Cardiac arrhythmia

The case series of 38 patients reported cardiac arrhythmia in 6 patients (4 patients had ventricular tachycardia, 1 patient had supraventricular tachycardia and 1 patient had atrial fibrillation)¹. Four of these patients had ECG synchronisation and 2 did not. All the arrhythmias resolved spontaneously except for atrial fibrillation in 1 patient which was treated by cardioversion. One of these patients developed bigeminy after resolution of ventricular tachycardia. The bigeminy resolved within 24 hours without treatment.

A case series of 21 patients reported transient ventricular tachycardia in 25% (7/28) of procedures². In 4 of the 7 procedures, arterial blood pressure was 'markedly decreased'.

A case series of 45 patients reported tachycardia 4 days after the procedure in 1 patient, which resolved³.

A case series of 18 procedures reported ventricular tachycardia associated with a fall in blood pressure in 1 patient: ECG synchronisation was not used in this patient⁴.

Pneumothorax

The case series of 45 patients reported pneumothorax in 14% (7/50) of procedures³. Six were treated with small calibre thoracostomy tubes (it was not stated whether patients were treated for lesions in the liver).

The case series of 38 patients reported pneumothorax in 4% (3/69) of procedures¹. One pneumothorax was related to liver ablation and a Heimlich valve was inserted with resolution 'in a few hours'.

The case series of 21 patients reported pneumothorax in 11% (3/28) of procedures². One occurred after transabdominal placement of electrodes in the liver.

The case series of 18 IRE procedures reported minor pneumothorax in 1 patient⁴.

Hypertension

The case series of 21 patients reported transient increases in systolic blood pressure of approximately 20 to 30 mm Hg after the treatment cycles in all patients².

The case series of 45 patients reported transient hypertension during the procedure in 1 patient³.

Biochemistry

The case series of 38 patients reported increases in the level of alanine aminotransferase (ALT) of between 19 and 1747 U/L 24 hours after 95% (40/42) of liver tumour ablation procedures (although a total of 49 procedures were performed for liver tumour ablation, ALT levels were not available for 7 procedures)¹. Levels returned to normal or baseline at 1-month follow-up in patients after 98% (39/40) of the procedures. One patient with progressive disease had an increased alanine aminotransferase level compared with baseline at 3-month follow-up. There were no increases in two procedures in which a review of output data from the IRE suggested that the current flow had not been generated.

The same case series reported transient increases in bilirubin level, which returned to normal or baseline levels at 1-month follow-up, in 18% (9/49) of liver tumour ablation procedures¹.

Brachial plexus injury

The case series of 38 patients reported upper-limb neurapraxia on recovery in 2 patients who had their arms extended above their head during the anaesthetic procedure for liver tumour ablation¹. One resolved at 1-month review and the other at 3-month review without further treatment.

The case series of 21 patients reported significant but transient neurapraxia on recovery in 17% (2/12 procedures) of patients who were positioned supine with their arms extended above their heads during the procedure².

Post-procedural pain

The case series of 21 patients reported postoperative pain in patients in 46% (13/28) of procedures².

Other complications

The case series of 21 patients reported contractions of the entire upper body, similar to that seen with a grand mal seizure, after each electrical pulse stimulation in inadequately paralysed patients (actual numbers not reported)². When patients were adequately paralysed, some muscular contractions were still visible, but they were mainly confined to the treatment area, sometimes including the diaphragm. These contractions were probably caused by direct muscle stimulation.

The case series of 18 IRE procedures reported partial collapse of the right upper lobe related to bronchial compression by the tumour in 1 patient⁴.

An analysis of 45 patients treated by irreversible electroporation for primary and secondary liver cancer, recorded in the Soft Tissue Ablation Register dataset, reported nine adverse events in 10% (5/51) of procedures⁷. These included acute renal failure, cholangitis caused by biliary stent occlusion, neurogenic bladder, abdominal pain, flank pain, dehydration, leukocytosis and urinary tract infection. All these resolved (with or without treatment).

Validity and generalisability of the studies

- Data only available from 2 case series.
- Of the 6 studies included, 4 are only available in conference abstract form. It is therefore difficult to assess the quality of these studies and the validity of the assessment measures used.
- Of the 6 studies included, 4 case series reported IRE performed in patients with either primary or secondary cancer, some in multiple sites (liver, lung, kidney, pelvis, lymph node and/or pancreas); however, outcomes are not reported separately. Consequently, it was not possible to identify safety and efficacy findings specifically for liver metastases.
- Information for the STAR dataset was obtained from an abstract sent by the director of the register. The abstract has not been published or presented anywhere.
- No long-term follow-up data available (longest follow-up: 3 months)
- The studies present limited evidence on efficacy of the procedure.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Microwave ablation for the treatment of liver metastases. NICE interventional procedures guidance 406 (2011). Available from www.nice.org.uk/guidance/IPG406
- Selective internal radiation therapy for non-resectable colorectal metastases in the liver. NICE interventional procedures guidance 401 (2011). Available from www.nice.org.uk/guidance/IPG401
- Cryotherapy for the treatment of liver metastases. NICE interventional procedures guidance 369 (2010). Available from www.nice.org.uk/guidance/IPG369
- Radiofrequency ablation for colorectal liver metastases. NICE interventional procedures guidance 327 (2009). Available from www.nice.org.uk/guidance/IPG327
- Laparoscopic liver resection. NICE interventional procedures guidance 135 (2005). Available from www.nice.org.uk/guidance/IPG135

Clinical guidelines

- Colorectal cancer: The diagnosis and management of colorectal cancer. NICE clinical guideline 131 (2011). Available from <http://www.nice.org.uk/guidance/CG131>
- Metastatic malignant disease of unknown primary origin: Diagnosis and management of metastatic malignant disease of unknown primary origin. NICE clinical guideline 104 (2010). Available from <http://www.nice.org.uk/guidance/CG104>

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Jonathan Evans, Edward Leen (Royal College of Radiologists), and Simon Olliff (British Society of Interventional Radiology)

- One Specialist Adviser suggested changing the title to ‘irreversible electroporation (IRE) for liver, lung, pancreatic, prostate tumours and extra-hepatic intra-abdominal/pelvic malignancies’.
- One Specialist Adviser said he performed the procedure regularly and 2 said they had never performed this procedure. One of the 2 said he may perform it in the future and that he was currently looking at performing a small series of cases at his hospital.
- One Specialist Adviser stated that the ablative therapy service he leads has incorporated IRE as part of its service over the last 10 months. He said they were currently carrying out an observational study to audit the safety and efficacy of the new technology in a selected group of patients.
- One Specialist Adviser considered the procedure to be a variation on an existing procedure (thermal-based ablation) with application of a higher voltage but linked with ECG synchronisation to ensure safety.
- Two Specialist Advisers considered the procedure to be definitely novel and of uncertain safety and efficacy. However, one Specialist Adviser stated that the procedure seemed to be safe with proper anaesthetic monitoring and ECG gating so it was the long-term efficacy that is uncertain at present. The Specialist Adviser noted that this is a needle type of ablation technique but different in some respects from better known techniques like radiofrequency ablation.
- Comparator: thermal based ablation techniques – radiofrequency ablation/microwave/cryoablation.
- Theoretical adverse events include cardiac dysrhythmias if (the procedure is performed) too close to the heart, puncture/damage of non-target organs, bowel perforation, sepsis, post ablation syndrome (the larger the volume of the ablation, the higher the risk), possibility of tumour seeding in needle track, bleeding, infection and complication of anaesthesia.
- Anecdotal adverse events include postablation syndrome (consists of flu-like symptoms and/or tiredness/lethargy lasting for 2–3 days, self-limiting).
- Adverse events reported in the literature include cardiac dysrhythmias and temporary neurapraxia as a result of arm extension during a prolonged period of anaesthesia.
- Key efficacy outcomes include patient survival time (including progression-free survival and overall survival), tumour destruction (based on imaging and markers if local), local tumour control/tumour recurrence rate and preservation of vascular and biliary structures.
- One Specialist Adviser stated that data on efficacy is limited. One Specialist Adviser noted that if IRE has the same effect on survival as RFA, it might then be better overall because of fewer side effects but this was unknown.
- Two Specialist Advisers stated that long-term efficacy and survival data is unknown and is needed. One Specialist Adviser stated that data is also needed on the use of the procedure in hypervascular tumours.
- One Specialist Adviser stated that access to general anaesthesia is needed. There should be access to anaesthetist, computed tomography (CT) or ultrasound.

- One Specialist Adviser stated that training for anyone intending to perform the procedure should include attending a local workshop to actually see the procedure. One Specialist Adviser stated that knowledge about operating the specific machine/generator and ECG gating was needed but this is supported by the company who supplies the machine and needles. Both Specialist Advisers noted that previous ablation experience was useful. They also said it was useful to have experience in targeting with image guidance (CT or ultrasound) and one Specialist Adviser said that 10 cases were needed to gain experience.
- One Specialist Adviser thought that the operator of the procedure should be competent in alternative treatments such as radiofrequency ablation, cryoablation and microwave ablation because these are the closest procedure type to IRE.
- One Specialist Adviser thought that the procedure should only be performed in units with a hepatopancreatobiliary specialist multidisciplinary team and that it should be audited.
- One Specialist Adviser thought that the procedure would have a moderate impact on the NHS and stated that the nature of the technology meant that it had the added advantage that it could be used in combination with systemic chemotherapy for the reversible electroporation component. The Specialist Adviser believed that IRE combined with chemotherapy would perform better than chemotherapy alone.
- One Specialist Adviser thought that the procedure would have a minor impact on the NHS initially but noted that this might change in 5 years or so if this ablation method was shown to be much better than others or vice versa.
- One Specialist Adviser thought that the procedure would have a minor impact on the NHS and was likely to be performed in fewer than 10 specialist centres in the UK because there were already good alternative ablative options for treating liver metastases.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- Future trials:
 - NCT01442324 Pilot Study of Irreversible Electroporation (IRE) to Treat Metastatic Liver Cancer & Cholangiocarcinoma: location: Italy; type: single-arm pilot clinical trial; estimated enrolment: 5 patients; estimated primary completion date: September 2012.
 - Two studies managed by the manufacturer of the IRE device are in progress:

- 1. NCT01078415 Pilot Study of Irreversible Electroporation (IRE) to Treat Early-Stage Primary Liver Cancer (HCC): locations: France, Germany, Italy and Spain; type: single-arm pilot clinical trial; estimated enrolment: 25 patients; estimated primary completion date: October 2011 (A first abstract on the primary endpoint of RECIST criteria has been accepted and will be presented at (Society of Interventional Radiology (SIR) meeting in March 2012); estimated study completion date: October 2013.
- 2. NCT01369420 NanoKnife Low Energy Direct Current (LEDC) System in Subjects With Locally Advanced Unresectable Pancreatic Cancer : location: Italy; type: single-arm pilot clinical trial; estimated enrolment: 10 patients; primary endpoint data are expected to become available in April 2012.
- In addition, several projects are run by investigators on IRE in cancer of the lung, prostate, liver and pancreas.
- Register:
 - The soft tissue ablation (STAR) register, USA will collect data on up to 200 patients across liver, pancreas, lung, prostate and kidney treatments, as well as other soft tissues.

References

1. Thomson KR, Cheung W, Ellis SJ et al. (2011) Investigation of the safety of irreversible electroporation in humans. *Journal of Vascular & Interventional Radiology* 22 (5): 611-21
2. Ball C, Thomson KR, Kavnoudias H (2010) Irreversible electroporation: a new challenge in "out of operating theater" anesthesia. *Anesthesia & Analgesia* 110 (5): 1305-9
3. Hays D, Robbins KV, Goodwin WJ et al. (2011) Single center, multiuser experience and safety of 50 Irreversible Electroporation (IRE) ablations [abstract]. *Journal of Vascular and Interventional Radiology*: vol. 22, no. 3, S80–S81.
4. Thomson KR, Cheung W, Ellis S et al. (2009) Irreversible electroporation with the NanoKnife in humans [abstract]. *CardioVascular and Interventional Radiology*: vol. 32, suppl. 2, p.407.
5. Kasivisvanathan V, Thapar A, Shalhoub J et al. (2011) Treatment of peri-portal colorectal liver metastasis using irreversible electroporation. *European Journal of Surgical Oncology*: vol. 37, issue 11, pp. 989–90.
6. Deepika K, Manjunath PS, Narayanan G (2011) Anesthetic management of a patient for nano knife surgery (Irreversible electroporation) [abstract]. *Anesthesia and Analgesia*: vol. 112 (5 suppl. 1).
7. Martin RCG (2012) 'Soft tissue ablation' (STAR) register data set. Obtained on 22 February 2012.

Appendix A: Additional papers on irreversible electroporation for the treatment of liver metastases

There were no additional papers identified.

Appendix B: Related NICE guidance for irreversible electroporation for the treatment of liver metastases

Guidance	Recommendations
Interventional procedures	Microwave ablation for the treatment of liver metastases. NICE interventional procedures guidance 406 (2011) 1.1 Current evidence on microwave ablation for the treatment of liver metastases raises no major safety concerns. The evidence on efficacy is inadequate in quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake microwave ablation for the treatment of liver metastases should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's efficacy and provide them with clear written information, including details about other treatment options. In addition, use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/guidance/IPG406/publicinfo). • Audit and review clinical outcomes of all patients having microwave ablation for the treatment of liver metastases (see section 3.1). 1.3 Patient selection should be carried out by a hepatobiliary cancer multidisciplinary team. 1.4 NICE encourages further research into microwave ablation for the treatment of liver metastases. Research should clearly define patient selection criteria and report tumour recurrence and patient survival. Comparison with other ablative techniques would be useful. NICE may review the procedure on publication of further evidence. Selective internal radiation therapy for non-resectable colorectal metastases in the liver. NICE interventional procedures guidance 401 (2011) 1.1 Current evidence on the safety of selective internal radiation therapy (SIRT) for non-resectable colorectal metastases in the liver is adequate. 1.2 The evidence on its efficacy in chemotherapy-naïve patients is inadequate in quantity. Clinicians should offer eligible patients who have not been previously treated by chemotherapy entry into well-designed research studies such as the FOXFIRE trial (www.octoxford.org.uk/alltrials/trials/FOXFIRE). For patients who are not

	eligible or who prefer not to enter a research trial, the procedure should be used with special arrangements for clinical governance, consent and audit. 1.3 For patients who have previously been treated with chemotherapy, there is evidence that SIRT can prolong time to progression of hepatic metastases, but more evidence is required on survival and quality of life (see section 1.7). Therefore for patients who have been previously treated with chemotherapy this procedure should be used with special arrangements for clinical governance, consent and audit. 1.4 Clinicians undertaking the procedure for patients outside research studies should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/guidance/IPG401/publicinfo). • Audit and review clinical outcomes of all patients having SIRT for nonresectable colorectal metastases (see section 3.1). 1.5 Patients should be selected for SIRT or entry into trials by a hepatobiliary cancer multidisciplinary team including an interventional radiologist, in liaison with a colorectal cancer multidisciplinary team. 1.6 SIRT should only be carried out by clinicians with specific training in its use and in techniques to minimise the risk of side effects of the procedure. 1.7 The Committee considered that SIRT is a potentially beneficial treatment for patients with non-resectable colorectal metastases in the liver, but that more research and data collection are required to demonstrate its efficacy. A recommendation about research trials for chemotherapy-naïve patients is given in 1.2 above. For patients who have previously been treated with chemotherapy, comparative trials are needed to determine whether SIRT prolongs survival compared with best standard treatment, and to determine its effect on quality of life. There is also a need to identify which subgroups of patients are likely to derive clinical benefit from SIRT. Research studies should clearly describe the characteristics of treated patients, and the extent and histological details of their tumours. Outcomes should include survival and quality of life. Downstaging of metastases allowing resection or ablation should be clearly documented. 1.8 NICE may review the procedure on publication of further
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	evidence. Cryotherapy for the treatment of liver metastases. NICE interventional procedures guidance 369 (2010) 1.1 Current evidence on the safety of cryotherapy for the treatment of liver metastases appears adequate in the context of treating patients whose condition has such a poor prognosis, but the evidence on efficacy is inadequate in quality. Therefore cryotherapy for the treatment of liver metastases should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake cryotherapy for the treatment of liver metastases should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand that other ablative treatments are available and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having cryotherapy for liver metastases (see section 3.1). 1.3 Patient selection and treatment should be carried out by a hepatobiliary multidisciplinary team with expertise in the use of ablative techniques Radiofrequency ablation for colorectal liver metastases. NICE interventional procedures guidance 327 (2009) 1.1 Current evidence on the safety and efficacy of radiofrequency (RF) ablation for colorectal liver metastases is adequate to support the use of this procedure in patients unfit or otherwise unsuitable for hepatic resection, or in those who have previously had hepatic resection, provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Patient selection should be carried out by a hepatobiliary cancer multidisciplinary team. Laparoscopic liver resection. NICE interventional procedures guidance 135 (2005) 1.1 Current evidence on the safety and efficacy of laparoscopic liver resection appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Patient selection for laparoscopic liver resection should be carried
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	out by a multidisciplinary team. Surgeons undertaking laparoscopic liver resection should have specialist training and expertise both in laparoscopic techniques and in the specific issues relating to liver surgery.
Clinical guidelines	Colorectal cancer: The diagnosis and management of colorectal cancer. NICE clinical guideline 131 (2011) The following recommendations have been identified as priorities for implementation. Diagnostic investigations • Offer colonoscopy to patients without major comorbidity, to confirm a diagnosis of colorectal cancer. If a lesion suspicious of cancer is detected, perform a biopsy to obtain histological proof of diagnosis, unless it is contraindicated (for example, patients with a blood clotting disorder). Staging of colorectal cancer • Offer contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis, to estimate the stage of disease, to all patients diagnosed with colorectal cancer unless it is contraindicated. No further routine imaging is needed for patients with colon cancer. • Offer magnetic resonance imaging (MRI) to assess the risk of local recurrence, as determined by anticipated resection margin, tumour and lymph node staging, to all patients with rectal cancer unless it is contraindicated. Preoperative management of the primary tumour • Do not offer short-course preoperative radiotherapy (SCPRT) or chemoradiotherapy to patients with low-risk operable rectal cancer (see table 1 for risk groups), unless as part of a clinical trial. Colonic stents in acute large bowel obstruction • If considering the use of a colonic stent in patients presenting with acute large bowel obstruction, offer CT of the chest, abdomen and pelvis to confirm the diagnosis of mechanical obstruction, and to determine whether the patient has metastatic disease or colonic perforation. Stage I colorectal cancer • The colorectal multidisciplinary team (MDT) should consider further treatment for patients with locally excised,

	pathologically confirmed stage I cancer, taking into account pathological characteristics of the lesion, imaging results and previous treatments. Imaging hepatic metastases - If the CT scan shows metastatic disease only in the liver and the patient has no contraindications to further treatment, a specialist hepatobiliary MDT should decide if further imaging to confirm surgery is suitable for the patient – or potentially suitable after further treatment – is needed. Chemotherapy for advanced and metastatic colorectal cancer - When offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer, consider one of the following sequences of chemotherapy unless they are contraindicated: - FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or - FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan^[1]) as second-line treatment or - XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment. Follow-up after apparently curative resection - Offer patients regular surveillance with: - a minimum of two CTs of the chest, abdomen, and pelvis in the first 3 years and - regular serum carcinoembryonic antigen tests (at least every 6 months in the first 3 years). Information about bowel function - Before starting treatment, offer all patients information on all treatment options available to them (including no treatment) and the potential benefits and risks of these treatments, including the effect on bowel function. ^[1] At the time of publication (November 2011), irinotecan did not have UK marketing authorisation for second-line combination therapy. Informed consent should be obtained and documented.
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	Metastatic malignant disease of unknown primary origin: Diagnosis and management of metastatic malignant disease of unknown primary origin. NICE clinical guideline 104 (2010) The following recommendations have been identified as priorities for implementation. The CUP team and its functions • Every hospital with a cancer centre or unit should establish a carcinoma of unknown primary (CUP) team, and ensure that patients have access to the team when malignancy of undefined primary origin (MUO) is diagnosed. The team should: ○ consist of an oncologist, a palliative care physician and a CUP specialist nurse or key worker as a minimum ○ have administrative support and sufficient designated time in their job plans for this specialist role and ○ have a named lead clinician. • Every hospital with a cancer centre or unit should assign a CUP specialist nurse or key worker to patients diagnosed with MUO or CUP. The CUP specialist nurse or key worker should: ○ take a major role in coordinating the patient's care in line with this guideline ○ liaise with the patient's GP and other community support services ○ ensure that the patient and their carers can get information, advice and support about diagnosis, treatment, palliative care, spiritual and psychosocial concerns ○ meet with the patient in the early stages of the pathway and keep in close contact with the patient regularly by mutual agreement and ○ be an advocate for the patient at CUP team meetings. • Refer outpatients with MUO to the CUP team immediately using the rapid referral pathway for cancer, so that all patients are assessed within 2 weeks of referral. A member of the CUP team should assess inpatients with MUO by the end of the next working day after referral. The CUP team should take responsibility for ensuring that a management plan exists which includes: ○ appropriate investigations ○ symptom control ○ access to psychological support and ○ providing information. • A CUP network multidisciplinary team (MDT) should be set up to review the treatment and care of patients with confirmed CUP, or with MUO or provisional CUP and complex diagnostic or treatment issues. This team should carry out established
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	specialist MDT responsibilities. Organisation of CUP services at network and national level • Every cancer network should establish a network site-specific group to define and oversee policies for managing CUP. The group should: ○ ensure that every CUP team in the network is properly set up (see recommendation 1.1.1.1) ○ ensure that the local care pathway for diagnosing and managing CUP is in line with this guideline ○ be aware of the variety of routes by which newly diagnosed patients present ○ advise the cancer network on all matters related to CUP, recognising that many healthcare professionals have limited experience of CUP ○ maintain a network-wide audit of the incidence of CUP, its timely management and patient outcomes ○ arrange and hold regular meetings for the group to report patient outcomes and review the local care pathway. Initial diagnostic phase • Offer the following investigations to patients with MUO, as clinically appropriate, guided by the patient's symptoms: ○ comprehensive history and physical examination including breast, nodal areas, skin, genital, rectal and pelvic examination ○ full blood count; urea, electrolytes and creatinine; liver function tests; calcium; urinalysis; lactate dehydrogenase ○ chest X-ray ○ myeloma screen (when there are isolated or multiple lytic bone lesions) ○ symptom-directed endoscopy ○ computed tomography (CT) scan of the chest, abdomen and pelvis ○ prostate-specific antigen (PSA) in men (see recommendation 1.2.2.1) ○ cancer antigen 125 (CA125) in women with peritoneal malignancy or ascites (see recommendation 1.2.2.1) ○ alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) (particularly in the presence of midline nodal disease) (see recommendation 1.2.2.1) ○ testicular ultrasound in men with presentations compatible with germ-cell tumours ○ biopsy and standard histological examination, with immunohistochemistry where necessary, to distinguish
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	carcinoma from other malignant diagnoses. Second diagnostic phase – special investigations - Do not use gene-expression-based profiling to identify primary tumours in patients with provisional CUP. When to stop investigations - Perform investigations only if: - the results are likely to affect a treatment decision - the patient understands why the investigations are being carried out - the patient understands the potential benefits and risks of investigation and treatment and - the patient is prepared to accept treatment. Selecting optimal treatment - Include the patient's prognostic factors in decision aids and other information for patients and their relatives or carers about treatment options. Chemotherapy in patients with confirmed CUP - If chemotherapy is being considered for patients with confirmed CUP, with no clinical features suggesting a specific treatable syndrome, inform patients about the potential benefits and risks of treatment.
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Appendix C: Literature search for irreversible electroporation for the treatment of liver metastases

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	19/01/2012	Issue 1 of 12, Jan 2012
Database of Abstracts of Reviews of Effects – DARE (CRD website)	20/01/2012	n/a
HTA database (CRD website)	20/01/2012	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	19/01/2012	Issue 1 of 12, Jan 2012
MEDLINE (Ovid)	19/01/2012	1946 – January Week 1 2012
MEDLINE In-Process (Ovid)	19/01/2012	January 18 2012
EMBASE (Ovid)	19/01/2012	1980 – 2012 Week 2
CINAHL (NLH Search 2.0/EBSCOhost)	20/01/2012	n/a

Trial sources searched on

- Current Controlled Trials *metaRegister* of Controlled Trials – *mRCT*
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

- 1 electroporation/ or electrochemotherapy/
- 2 (irreversibl* adj3 (electropor* or electropermeab* or electro-por*
or electro-permeab*)).tw.
- 3 (electric* adj1 field* adj3 (pulse* or cell? or membrane* or
pore?)).tw.
- 4 (bipolar adj3 (pulse? or electro* or mode?)).tw.
- 5 ire.tw.
- 6 nanoknife.tw.
- 7 or/1-6
- 8 exp neoplasms/
- 9 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or
tumour* or tumor* or malignan* or metastas*).tw.
- 10 or/8-9
- 11 7 and 10
- 12 Product Surveillance, Postmarketing/
- 13 (adverse adj3 (event? or reaction? or effect? or outcome?)).tw.
- 14 ((side or undesirable) adj3 effect?).tw.
- 15 (safe or safety or harm or harms or harmful or complication\$ or
risk or risks).ti.
- 16 or/12-15
- 17 7 and 16
- 18 11 or 17
- 19 animal/ not human/
- 20 18 not 19